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"CHIRAL ARYLKETONES IN THE TREATMENT OF NEUTROPHIL-DEPENDENT INFLAMMATORY DISEASES"

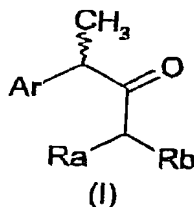
The present invention relates to chiral arylketones, a process for their preparation, and pharmaceutical compositions containing them, which are useful in the prevention and treatment of tissue damage due to the exacerbated recruitment of polymorphonucleate neutrophils in the inflammatory sites.

Other classes of compounds, such as R-2-arylpropionic acid amides and N-acylsulfonamides useful in the prevention and treatment of tissue damage due to the exacerbated recruitment of polymorphonucleate neutrophils in the inflammatory sites, have been described in WO 01/58852 and WO 00/24710 respectively.

The compounds of the invention are generally known compounds and disclosed in Belstein Handbook of Organic Chemistry.

Detailed description of the invention

More specifically, the present invention relates to chiral arylketones of general formula I:



wherein:

Ar is an aryl group;

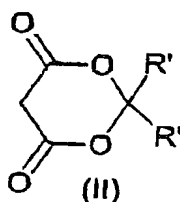
Ra and Rb are independently chosen in the group of hydrogen, linear or branched C₁-C₆ alkyl, phenyl, α- or β-naphthyl, 2, 3, 4-pyridyl, C₁-C₄-alkylphenyl, C₁-C₄-alkyl(α- or β-naphthyl), C₁-C₄-alkyl(2, 3, 4-pyridyl), cyano (-CN), carboxamide, carboxyl or carboxyesters of formula CO₂R" wherein R" is the residue of a linear or branched C₁-C₆ aliphatic alcohol, a phosphonate PO(OR")₂ wherein R" is as defined above, a group of formula di-X-(CH₂)_n-Z, wherein X is a CO, SO, SO₂ group; Z is H, *tert*-butyl, isopropyl, CO₂R", CN, phenyl, α- or β-naphthyl, 2, 3, 4-pyridyl, C₃-C₆ cycloalkyl, NH-BOC, NH₂;

n is zero or an integer from 1 to 3; or Ra and Rb, with the carbon atom to which they are bound, form a cyclic residue 4, 6-dioxo-1, 3-dioxanyl-2, 2-disubstituted of formula II:

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branched C₁-C₆ aliphatic alcohol, a phosphonate PO(OR'')₂ wherein R'' is as defined above, a group of formula -X-(CH₂)_n-Z, wherein X is a CO, SO, SO₂ group; Z is H, *tert*-butyl, isopropyl, CO₂R'', CN, phenyl, α- or β-naphthyl, 2, 3, 4-pyridyl, C₃-C₆ cycloalkyl, NH-BOC, NH₂; n is zero or an integer from 1 to 3; or Ra and Rb, with the carbon atom to which they are bound, form a cyclic residue 4, 6-dioxo-1, 3-dioxanyl-2, 2-disubstituted of formula II:



wherein R' is methyl or ethyl, or the two groups R' form a cyclohexane or cyclopentane ring,

in the preparation of a medicament for the treatment of diseases that involve IL-8 induced human PMNs chemotaxis.

2. Use of compounds according to claim 1 wherein Ar represents a residue 4-isobutyl-phenyl, 3-benzoyl-phenyl, 5-benzoyl-phenyl, 2-acetoxy-phenyl, 3-phenoxy-phenyl.
3. Use of compounds according to claims 1 or 2 selected from:

methyl (R)(-)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

methyl (S)(+)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

(R,S) 4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid;

methyl (R)(-)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

(R)(-)-3-[(4'-isobutyl)phenyl]butan-2-one;

(S)(+)-3-[(4'-isobutyl)phenyl]butan-2-one;

(R)(-)-3-[(3'-benzoyl)phenyl]butan-2-one;

(R)(-)-dimethyl 3-(4-isobutyl-phenyl)-2-oxobutan-1-phosphonate;

(S)(+)-dimethyl 3-(3'-phenoxy-phenyl)-2-oxo-butyl-1-phosphonate;

(R)(-)-2-(4-isobutylphenyl)-pentan-3-one;

(S)(+) ethyl-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

(S)(+)-3-[(3'-benzoyl)phenyl]butan-2-one;

(R)(-)-2-(4-isobutylphenyl)-4-phenyl-butan-3-one;

(R)(-)-2-(4-isobutylphenyl)-5-phenyl-pentan-3-one;

(R)(-)-2-(4-isobutylphenyl)-5-(pyrid-3-yl)-pentan-3-one;

(R,S) 5-(4'-isobutylphenyl)-hexan-2, 4-dione;

(R,S) 1-phenyl-5-(4'-isobutylphenyl)-2, 4-hexandione;

5 (R,S) 1-(pyrid-2-yl)-4-(4'-isobutylphenyl)-1, 3-pentadione;

(R) (-) 2-(4-isobutylphenyl)-7-*tert*-butoxycarbonylamino-heptan-3-one;

(R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, methyl-sulfoxide;

(R,S) 2-(3'-benzoylphenyl)-3-oxo-butyl, methyl-sulfoxide;

(R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, methyl-sulfone;

10 (R,S) 2-(3'-benzoylphenyl)-3-oxo-butyl, methyl-sulfone;

(R,S) 2-(3'-phenoxyphenyl)-3-oxo-butyl, methyl-sulfone;

(R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, phenyl-sulfone;

(R)(-)-4-(4'-pyridyl)-2-[(4"-isobutyl)phenyl]butan-3-one;

(R) (+)-5-[2-(4-isobutyl-phenyl)-propion-1-yl]-2, 2-dimethyl-1,3-dioxan-4, 6-dione;

15 (R) (-)-5-[2-(3'-benzoyl-phenyl)-propion-1-yl]-2, 2-dimethyl-1,3-dioxan-4, 6-dione.

(R)-2-[4-(1-oxo-2-isoindoliny)phenyl]-3-oxo-valeramide;

(R)-2-[4-(1-oxo-2-isoindoliny)phenyl]-3-oxo-valeronitrile;

4. Use of compounds:

(R)(-) methyl 4-[(4'-benzoyloxy)phenyl]-3-oxopentanoate,

20 (R)(-) methyl-4-[(4'-isopropylsulfonyloxy)phenyl]-3-oxopentanoate and

(R)(-) methyl-4-[[4'-(2"-ethyl)phenylsulfonylamino]phenyl]-3-oxopentanoate,

in the preparation of a medicament for the treatment of diseases that involve IL-8 induced human PMNs chemotaxis.

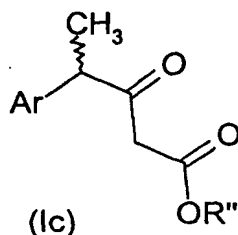
25 5. Use of compounds according to Claims 1 or 2, wherein the steric configuration of the carbon atom to which the residue Ar is bound corresponds to the enantiomer (R).

6. Pharmaceutical compositions containing a compound according to any one of Claims 1 to 5 in admixture with a suitable carrier thereof.

30 7. Use of the compounds according to any one of Claims 1 to 5 in the preparation of medicaments for the treatment psoriasis, rheumatoid arthritis, ulcerative colitis, acute respiratory distress syndrome (ARDS), idiopathic fibrosis,

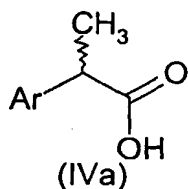
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glomerulonephritis, bullous pemphigo and for the prevention and the treatment of damages caused by ischemia and reperfusion.



A β -ketoester of formula Ia and Ic may optionally be dealkoxydecarboxylated to the
5 corresponding arylketone of formula I by simply heating in an aprotic solvent (preferably dimethylsulfoxide) in the presence of small amounts of water and, optionally, of small amounts of electrolytes, such as NaCl, NaCN, LiCl, LiI (according to J.P. Krapcho, Synthesis 805 and 893, 1982, and references cited herein). Likewise, using well known
10 methods, a compound of formula Ia can be converted into another compound of formula I by removal of any protective groups that may be present, or by saponification of carboxyl groups, or by conversion of nitriles into carboxyamides.

The compounds of formula IV are obtained in a conventional way, conserving their enantiomeric integrity, starting from the individual enantiomers of the 2-aryl-propionic acids of formula IVa:



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which are known compounds and can be obtained from the individual racemates using known methods of optical resolution.

The preparation of the carbanions of formula V consists in a process of C-acylation in virtually neutral conditions, fully described in the literature (see, for example, D. W. Brooks *et al.*, Angew. Chem. Int. Ed. Engl., 18, 72, 1979), as well as monoesters of
20 malonic acids and of monosubstituted malonic acids, also on sulfinylacetic acids, sulfonylacetic acids and phosphonoacetic acids. All these acids are known in the literature or can be prepared using known methods, such as monosaponification of diesters of

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5 Brooks *et al.*, *Angew. Chem. Int. Ed. Engl.*, 18, 72, 1979), as well as monoesters of malonic acids and of monosubstituted malonic acids, also on sulfinylacetic acids, sulfonylacetic acids and phosphonoacetic acids. All these acids are known in the literature or can be prepared using known methods, such as monosaponification of diesters of malonic acids and their monosubstituted analogues or saponification of phosphonoacetic
10 acids and 2-substituted analogues; sulfinylacetic and sulfonylacetic acids may be obtained by oxidation of ethers of thioglycolic acid. Alternatively, it is possible to use lithium enolates of formula V, obtained by reaction of lithium alkyls with known alkyl esters of alkylphosphonates (see, for example, N. Mongelli *et al.*, *Synthesis*, 310, 1988) or with esters of acetic acid (according to D.H. Harris *et al.*, *Tetrah. Lett.*, 28, 2837, 1987).

15 For the preparation of enolates of formula Va, and more generally for the procedure of acylation of the cyclic alkylidenesters of malonic acid (also known as Meldrum acids) with the activated species of a carboxyl of formula IV, the method described by Y. Oikawa *et al.*, *J. Org. Chem.*, 43, 2087 (1978), R.P. Houghton and D.J. Lapham, *Synthesis* 451 (1982) and C.C. Chan and X. Hung, *ibidem*, 452 (1982) is used.

20 The preparation of dialkoxyphosphonoacetic acids and that of their esters are exemplified in US 4151172 (April 24, 1979), or described by R.A. Malevannaya *et al.*, in *Zh. Obshch. Khim.* 41, 1426 (1971).

Specific examples of the compounds of the invention are:

methyl (R)(-)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

25 methyl (S)(+)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate;

(R,S) 4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid;

methyl (R)(-)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

(R)(-)-3-[(4'-isobutyl)phenyl]butan-2-one;

(S)(+)-3-[(4'-isobutyl)phenyl]butan-2-one;

30 (R)(-)-3-[(3'-benzoyl)phenyl]butan-2-one;

(R)(-)-dimethyl 3-(4-isobutyl-phenyl)-2-oxobutan-1-phosphonate;

(S)(+)-dimethyl 3-(3'-phenoxy-phenyl)-2-oxo-butyl-1-phosphonate;

- (R)(-) methyl-4-{[4'-(2"-ethyl)phenylsulfonylamino]phenyl}-3-oxopentanoate;
 (R,S) 5-(4'-isobutylphenyl)-hexan-2, 4-dione;
 (R,S) 1-phenyl-5-(4'-isobutylphenyl)-2, 4-hexandione;
 (R,S) 1-(pyrid-2-yl)-4-(4'-isobutylphenyl)-1, 3-pentadione;
 5 (R) (-) 2-(4-isobutylphenyl)-7-*tert*-butoxycarbonylamino-heptan-3-one;
 (R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, methyl-sulfoxide;
 (R,S) 2-(3'-benzoylphenyl)-3-oxo-butyl, methyl-sulfoxide;
 (R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, methyl-sulfone;
 (R,S) 2-(3'-benzoylphenyl)-3-oxo-butyl, methyl-sulfone;
 10 (R,S) 2-(3'-phenoxyphenyl)-3-oxo-butyl, methyl-sulfone;
 (R,S) 2-(4'-isobutylphenyl)-3-oxo-butyl, phenyl-sulfone;
 (R)(-)-4-(4'-pyridyl)-2-[(4"-isobutyl)phenyl]butan-3-one;
 (R)-2-[4-(1-oxo-2-isoindoliny)phenyl]-3-oxo-valeramide;
 (R)-2-[4-(1-oxo-2-isoindoliny)phenyl]-3-oxo-valeronitrile;
 15 (R) (+)-5-[2-(4-isobutyl-phenyl)-propion-1-yl]-2, 2-dimethyl-1, 3-dioxan-4, 6-dione;
 (R) (-)-5-[2-(3'-benzoyl-phenyl)-propion-1-yl]-2, 2-dimethyl-1, 3-dioxan-4, 6-dione.

The compounds of formula I are powerful inhibitors of the chemiotaxis of the neutrophils induced by IL-8 and inhibit the amplification of the production of TNF- α stimulated by lipopolysaccharides and by hydrogen peroxide. An exacerbated production of hydrogen
 20 peroxide is notoriously the final consequence of the neutrophilic activation consequent upon a chemiotactic stimulus.

Examples of β -ketoesters of formula I are methyl R(-)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate and methyl R(-)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate, which, at the concentration of 10^{-8} M, inhibit the chemiotaxis of human neutrophils to an extent higher
 25 than 50% as compared to control values.

A typical example of 2-aryl-alkan-3-one is R(-)-3-[(4'-isobutyl)phenyl]butan-2-one for which an IC_{50} of $5 \cdot 10^{-10}$ M has been calculated in the same *in vitro* inhibition assay.

For evaluation of the compounds of the invention, polymorphonucleated blood cells were used obtained from heparinized blood of healthy adult volunteers by means of
 30 sedimentation on dextran. The mononucleated cells were removed by means of Ficoll/Hypaque, whilst the red blood cells were eliminated by treatment with hypotonic solutions. The cell vitality of the polymorphonucleated leucocytes (PMNs) was calculated

by means of exclusion with Turk and Trypan Blue whilst after staining with Diff Quinck the percentage of the PM-nucleates on the cytocentrifugate was estimated (for details of the experimental techniques used see W.J. Ming *et al.*, J. Immunol., 138, 1469, 1987).

5 In each of the *in vitro* experiments, time periods of 10 minutes were used for the incubation of the PMNs with the compounds of the invention, operating at a temperature of 37°C.

10 In the experiments of chemiotaxis and in those designed for measuring the cytosol levels of the Ca^{2+} ion, human recombinant IL-8 (Pepro Tech.) was used as stimulant: the liophilized protein was dissolved in HBSS (Hank's balanced salts solution) at a concentration of 100 ng/mL and was used after dilution in HBSS down to concentrations of 10 ng/mL in the chemiotaxis experiments and at the concentration of 25-50 ng/mL in the evaluation of the modifications of $[\text{Ca}^{2+}]_i$.

15 In the chemiotaxis assay (according to W. Falket *et al.*, J. Immunol. Methods, 33, 239, 1980) PVP filters were used having a porosity of 5 μm and a Plexiglas microchamber suitable for making 48 replications. The microchamber consists of a block of Plexiglas containing 48 wells, each having a capacity of 25 μL and is provided with a lid, which in turn contains 48 pores arranged in such a way that, once the lid has been set in place and screwed to the underlying part, it comes to form the top compartments of the microchamber, each having a capacity of 50 μL .

20 The compounds under study were added at one and the same concentration in the wells of higher level, which contain the suspension of PMNs and in the wells of lower level, which contain the vehicle to which IL-8 (or a different stimulant) has been added or not.

25 For determination of the cytosol variations of the $[\text{Ca}^{2+}]_i$, the experimental model described by C. Bizzarri *et al.*, (Blood, 86, 2388, 1995) was adopted, using slides containing adhered PMNs, which were fed with 1 μM of Fura-2AM in order to evaluate said variations of $[\text{Ca}^{2+}]_i$ in real time. In turn, cytocentrifugates of PMNs were resuspended in RPMI medium 1640 with 5% of FCS (foetal cow serum) at a concentration of $3 \times 10^6/\text{mL}$ and then plated on round glass slides of a diameter of 25 mm, which were placed in an incubator for 30 min at 37°C. After three consecutive washings with balanced salts solution (BSS) to
30 remove the non-adherent cells, a further incubation was performed for the set of adherent cells for a maximum of 4 hours before feeding with Fura-2AM.

The compounds of the invention prevent the increase in the intracellular concentration of Ca^{2+} induced by IL-8.

The compounds of the invention are characterized by their capacity for inhibiting *in vitro* the chemotaxis of the human PMN leucocytes (PMNs) stimulated by interleukin 8, also known as "monocyte-derived neutrophil-activating protein" (NAP/IL-8 or more simply IL-8). Said inhibition is dose-dependent, with values of IC_{50} (dose inhibiting 50% of the effect) in the 10^{-7} to 10^{-9} -M range; the inhibiting effect is selective and specific in regard to the chemiotactic stimulus induced by IL-8. Concentrations higher by one or two orders of magnitude are needed to inhibit the chemotaxis stimulated *in vitro* by other chemiotactic factors (C5a, formylpeptides of bacterial origin or synthetic origin, such as f-LMP). The specificity of the compounds of the invention is moreover demonstrated by their capacity to inhibit the increase in the intracellular concentration $[\text{Ca}^{2+}]_i$ in human PMNs, an increase that is associated to the activation of the human PMNs themselves by IL-8 [J.H. Liu *et al.*, J. Infect. Dis., 166, 1089 (1992)].

Independently of the absolute configuration, the compounds of the invention are without significant effects on cyclooxygenasis and on the production of PG.

In fact, in murine macrophages stimulated by LPS ($1\text{ }\mu\text{g/mL}$), the compounds of the invention (evaluated in the range of concentration of 10^{-5} to 10^{-7} M) show an inhibition of the production of PGE_2 which, albeit frequently at the limit of statistical significance, is never higher than 10 to 15% of the basal value.

The above minor inhibition of the synthesis of PGE_2 involves the advantage, unlike what occurs for certain 2-aryl-propionic acids, of not constituting a stimulus that is likely to amplify the synthesis of $\text{TNF-}\alpha$ by the murine macrophages themselves (once they have been stimulated by LPS). The amplification of the synthesis of $\text{TNF-}\alpha$ is considered to concur, in turn, in amplifying the activation and chemotaxis of the neutrophils and the synthesis of IL-8. On the other hand, these effects of non-amplification of the synthesis of $\text{TNF-}\alpha$ are shown also in regard to the synthesis of $\text{TNF-}\alpha$ stimulated by hydrogen peroxide.

It is known that interleukin 8 (IL-8) and the correlated cytokines are the most important modulators of the infiltration of the neutrophils in diseases such as psoriasis (B.J. Nickoloff *et al.*, Am. J. Pathol., 138, 129, 1991), rheumatoid arthritis (M. Selz *et al.*, J. Clin. Invest. 87, 463, 1991), ulcerative colitis (Y.R. Mahkila *et al.*, Clin. Sci., 82, 273,

Nickoloff *et al.*, Am. J. Pathol., 138, 129, 1991), rheumatoid arthritis (M. Selz *et al.*, J. Clin. Invest. 87, 463, 1991), ulcerative colitis (Y.R. Mahkla *et al.*, Clin. Sci., 82, 273, 1992), acute respiratory distress syndrome (ARDS), idiopathic fibrosis (P.C. Carré *et al.*, J. Clin. Invest., 88, 1802, 1991 and E.J. Miller *et al.*, Am. Rev. Respir. Dis., cited above),
5 glomerulonephritis (T. Wada *et al.*, J. Exp. Med., 180, 1135, 1994) and bullous pemphigo. The compounds of the invention are then used for the treatment of said diseases, conveniently formulated in pharmaceutical compositions using conventional techniques and excipients.

The compounds of the invention are also conveniently used for the prevention and the
10 treatment of damages caused by ischemia and reperfusion, in particular in connection with organ transplantation.

The compositions of the invention can be administered via intramuscular injection, via intravenous route, as a bolus, in preparations for dermatological use (creams, lotions, sprays and ointments), as well as via oral route in the form of capsules, tablets, syrup,
15 controlled-release formulations, and the like.

The mean daily dosage will depend upon various factors, such as the severity of the illness and the conditions of the patient (age, sex and weight). The dose will vary generally from one mg or a few mg up to 1500 mg of the compounds per day, optionally divided into multiple administrations. Higher dosages, as well as more prolonged treatment times, can
20 be administered also by virtue of the low toxicity of the compounds of the invention.

The following examples are provided by way of illustration of the invention. The examples are not construed to be viewed as limiting the scope of the invention.

Example I

(R) (-)-3-[(4'-isobutyl)phenyl]butan-2-one

25 (R) (-)-ibuprofen (2g, 9.69 mmol) is dissolved in thionyl chloride (4 mL), and the solution obtained is refluxed for 4 hours.

After cooling to room temperature, the solvent is evaporated at reduced pressure, and the excess of thionyl chloride is eliminated by dissolving the residue twice with dioxane and evaporating the solvents at a high vacuum. The oily yellow residue (2.34 g; 9.34 mmol)
30 thus obtained, is dissolved in dry dichloromethane (3 mL) and added, by means of slow dripping and in an inert-gas atmosphere, to a solution of 2, 2-dimethyl-1, 3-dioxan-2, 5-dione (Meldrum's acid) (1.35 g; 9.34 mmol) and pyridine (1.83 mL; 22.9 mmol) in dry dichloromethane (7.5 mL) previously cooled to 0 - 5°C with a water/ice bath. Once the

additions are completed, the product is left for one hour at this temperature and then for another hour at room temperature. The mixture diluted with dichloromethane is partitioned with a 2N HCl and crushed ice, under vigorous stirring for 30 min. After separation of the phases, the organic phase, washed with 2N HCl (2x10 mL) and with a saturated solution of NaCl, is dried on Na₂SO₄. After evaporation of the solvents at reduced pressure, 2.69 g of R(+)-5-[2-(4-isobutyl-phenyl)-propion-1-yl]-2, 2-dimethyl-1, 3-dioxan-4, 6-dione is obtained as an oil. ([α _D] = + 61.7°; c = 1% CH₂Cl₂) which, without further purifications, is dissolved in dioxane (10 mL). Glacial acetic acid (0.84 mL) and water (0.13 mL) are added, and the resulting solution is heated to the reflux temperature for 3 hours. After cooling and evaporation of the solvents, the residue is purified by means of flash chromatography (eluent: n-hexane/ethyl ether 9:1) to yield (R) (-)-3-[(4'-isobutyl)phenyl]butan-2-one as a pale yellow oil (0.97 g; 4.75 mmol).

[α]_D = -216.1° (c=1; CH₃CH₂OH); ¹H-NMR (CDCl₃): δ 6.95 (s, 4H); 3.61 (q, 1H, J=8Hz); 2.3 (d, 3H, J=7Hz); 1.93 (s, 3H); 1.75 (m, 1H); 1.26 (d, 2H, J=8Hz); 0.85 (d, 6H, J=7Hz).

Example 2

(S) (+)-3-[(4'-isobutyl)phenyl]butan-2-one;

(R) (-)-3-[(3'-benzoyl)phenyl]butan-2-one;

Following the procedure of Example 1, using 0.3 g (1.33 mmol) of S (+)-ibuprofen, S(+)-3-[(4'-isobutyl)phenyl]butan-2-one is obtained (0.13 g, 0.63 mmol) as a pale yellow oil; [α]_D = +210.5 (c=1; CH₃CH₂OH); ¹H-NMR (CDCl₃): δ 7.10 (s, 4H); 3.75 (q, 1H, J=8Hz); 2.45 (d, 3H, J=7Hz); 2.05 (s, 3H); 1.85 (m, 1H); 1.32 (d, 2H, J=8Hz); 0.92 (d, 6H, J=7Hz).

Likewise, starting from 0.74 g (2.9 mmol) of (R) (-)-ketoprofen, 0.46 g (1.79 mmol) of R(-)-3-[(3'-benzoyl)phenyl]butan-2-one are obtained as a yellow oil; [α]_D = -103° (C=1; CH₃OH); ¹H-NMR (CDCl₃): δ 7.85 (m, 2H); 7.75 (m, 2H); 7.60 (m, 1H); 7.55-7.40 (m, 4H); 3.85 (q, 1H, J=8Hz); 2.1 (s, 3H); 1.45 (d, 3H, J=8Hz).

Example 3

methyl (R) (-)-4-[(4'-isobutyl)phenyl]-3-oxopentanoate

4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid

(R) (-)-ibuprofen (1.2 g, 5.8 mmol) is dissolved in dioxane (5 mL); thionyl chloride (2.36 mL) is added and the solution obtained is refluxed and left to reflux for 3 hours. After cooling to room temperature, the solvent is evaporated at reduced pressure, and the excess of thionyl chloride is eliminated, dissolving the residue twice with dioxane and

evaporating the solvents under high vacuum. An oily yellow residue (1.3 g; 5.79 mmol) is obtained, which is dissolved in dry dichloromethane (2 mL) and added, by means of slow dripping and in an inert atmosphere, to a solution of 2, 2-dimethyl-1,3-dioxan-2,5-dione (Meldrum's acid) (0.83 g; 5.79 mmol) and pyridine (1.12 mL; 14 mmol) in dry dichloromethane (5 mL) previously cooled to $T=+5^{\circ}\text{C}$ with a water/ice bath. Once the additions are completed, the mixture is left for one hour at this temperature and then for another hour at room temperature. The mixture, diluted with dichloromethane is repartitioned with a 2N solution of HCl and crushed ice, under vigorous stirring for approximately 30 min. After separation of the phases, the organic phase, washed with 2N HCl (2 x 10 mL) and with a saturated solution of NaCl, is dried on Na_2SO_4 . After evaporation of the solvent at reduced pressure, the residue of (R) (+)-5-[2-(4-isobutylphenyl)-propion-1-yl]-2, 2-dimethyl-1, 3-dioxan-4, 6-dione ($[\alpha]_{\text{D}}=+62^{\circ}$; $c=1.1\%$ CH_2Cl_2) without further purifications, is dissolved in methanol (14 mL); the solution is reheated to reflux for 3 hours. After cooling and evaporation of the solvent, the residue is purified by means of flash chromatography (eluent: n-hexane/ethyl ether 8:2) to yield pure methyl ester of (R) (-)-4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid as a colourless oil (0.6 g; 2.28 mmol); $[\alpha]_{\text{D}}=-192.5^{\circ}$ ($c=1$; CH_3OH); $^1\text{H-NMR}$ (CDCl_3): δ 7.1 (s, 4H); 3.88 (q, 1H, $J=8\text{Hz}$); 3.67 (s, 3H); 3.47-3.28 (q, 2H, $J=8\text{Hz}$); 2.45 (d, 2H, $J=8\text{Hz}$); 1.85 (m, 1H); 1.40 (d, 3H, $J=8\text{Hz}$); 0.95 (d, 6H, $J=7\text{Hz}$).

To a solution in methanol (2 mL) of 0.15 g (0.57 mmol) of said ester is added a solution of 1N NaOH (1 mL); and the mixture is stirred at room temperature overnight. The solvents are then evaporated at reduced pressure; the residue is dissolved with water (3 mL), and 2N HCl is added by dripping up to $\text{pH}=1$ the mixture is then extracted with ethyl ether (3x10 mL); the organic phase is then washed with a saturated solution of NaCl (10 mL), dried on Na_2SO_4 , and evaporated at reduced pressure to yield 0.12 g (0.48 mmol) of pure (+) 4-[(4'-isobutyl)phenyl]-3-oxopentanoic acid, as a colourless oil; $^1\text{H-NMR}$ (CDCl_3): δ 7.1 (m 4H); 3.88 (q, 1H, $J=8\text{Hz}$); 3.45 (m, 2H); 2.48 (d, 2H, $J=8\text{Hz}$); 1.90 (m, 1H); 1.45 (d, 3H, $J=8\text{Hz}$); 0.90 (d, 6H, $J=7\text{Hz}$).

Example 4

30 methyl (R) (-)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate.

By substituting the R-ibuprofen with 0.74 g (2.9 mmol) of R(-)-ketoprofen in the process of Example 3, 0.81 g of (R) (-)-5-[2-(3'-benzoyl-phenyl)-propion-1-yl]-2,2-dimethyl-1,3-

dioxan-4,6-dione are obtained ($[\alpha]_D = -39.5^\circ$; $c=1\%$ CH_2Cl_2), which, by boiling in methanol yields, after purification by flash chromatography (eluent: n-hexane/ethyl acetate 8:2), 0.49 g (1.56 mmol) of pure methyl (R) (-)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate as a colourless oil, $[\alpha]_D = -135^\circ$ ($c=1$; CH_3OH); $^1\text{H-NMR}$ (CDCl_3): δ 7.85-7.40 (m, 9H); 4.0 (q, 1H, $J=8\text{Hz}$); 3.70 (s, 3H); 3.50-3.30 (q, 2H, $J=8\text{Hz}$); 1.45 (d, 3H, $J=8\text{Hz}$).

Example 5

(S) (+) ethyl-4-[(3'-benzoyl)phenyl]-3-oxopentanoate

(S) (+)-3-[(3'-benzoyl)phenyl]butan-2-one

At room temperature, in an inert-gas atmosphere and under stirring, to a suspension of magnesium ethylate (0.57 g) in 6 mL of anhydrous THF a solution of mono-ethylester malonic acid (1.3 g) in 3 mL of THF is added. After complete solution of the reagents, to the mixture of the complex magnesium-malonic ethylester, by rapid dripping, a solution of S(+) 2-(3-benzoylphenyl) propionylimidazolidine (0.83 g) in 10 mL of anhydrous THF is added, prepared *in situ* by addition of 0.43 g of 1,1'-carbonyldiimidazole to a solution of S(+) 2-(3-benzoylphenyl) propionic acid (0.66 g) in THF. The mixture is stirred for 4 hours, then is acidified by addition of 50% aqueous AcOH (1.2 mL) and is concentrated under vacuum at a small volume and diluted with water. After repeated extractions with ethyl acetate, the organic phases are combined, rinsed with a saturated solution of NaCl, dried on sodium sulfate, and evaporated to dryness to yield, after purification on silica gel, 0.82 g of ethyl (S) (+)-4-[(3'-benzoyl)phenyl]-3-oxopentanoate;

$[\alpha]_D = +129^\circ$ ($c=1$; CH_3OH); $^1\text{H-NMR}$ (CDCl_3): δ 7.82-7.45 (m, 9H); 4.1 (q, 1H, $J=8\text{Hz}$); 3.75 (s, 3H); 3.50-3.25 (q, 2H, $J=8\text{Hz}$); 1.48 (d, 3H, $J=8\text{Hz}$)

According the same described procedure and starting from the corresponding arylpropionic acids the following 3-oxoesters have been synthesised:

(R)(-) methyl 4-[(4'-benzoyloxy)phenyl]-3-oxopentanoate

$^1\text{H-NMR}$ (CDCl_3): δ 8.02 (m, 2H); 7.51 (m, 1H); 7.35 (m, 2H); 7.27 (s, 1H); 7.22 (m, 2H); 3.85 (m, 2H); 3.74 (s, 3H); 3.42-3.37 (q, 2H, $J=8\text{Hz}$); 2.78 (q, 2H, $J=8\text{Hz}$); 1.25 (t, 3H, $J=8\text{Hz}$).

(R)(-) methyl-4-[(4'-isopropylsulfonyloxy)phenyl]-3-oxopentanoate

$[\alpha]_D = -184.2^\circ$ ($c=1$; CH_3OH); $^1\text{H-NMR}$ (CDCl_3): δ 7.32 (d, 2H, $J=7\text{Hz}$); 7.21 (d, 2H, $J=7\text{Hz}$); 4.1 (q, 1H, $J=8\text{Hz}$); 3.81 (m, 1H); 3.70 (s, 3H); 3.50-3.30 (q, 2H, $J=8\text{Hz}$); 1.75 (d, 6H, $J=7\text{Hz}$); 1.45 (d, 3H, $J=8\text{Hz}$).

(R)(-) methyl-4-{{[4'-(2"-ethyl)phenylsulfonylamino]phenyl}-3-oxopentanoate

[α]_D = -81.3° (c=1; CH₃OH); ¹H-NMR (CDCl₃): δ 7.32 (d, 2H, J=7Hz); 7.20 (m, 6H); 6.84 (bs, 1H, SO₂NH); 4.05 (q, 1H, J=8Hz); 3.72 (s, 3H); 3.55-3.35 (q, 2H, J=8Hz); 2.75 (q, 2H, J=8Hz); 1.45 (d, 3H, J=8Hz); 1.22 (t, 3H, J=8Hz). A solution of 0.4 g of the compound
5 in 1.5 mL of dimethylsulfoxide, to which 2 drops of a saturated aqueous solution of NaCl are added, is heated for 4 hours, under stirring, in a bath at 140-145°C; after cooling and dilution with water, the mixture is extracted repeatedly with ethyl acetate. From the combined organic phases, after the usual processing, an oily residue is obtained which, after purification by flash chromatography, yields 0.24 g of S (+)-3-[(3'-
10 benzoyl)phenyl]butan-2-one as a yellow oil; [α]_D = +101° (c=1; CH₃OH); ¹H-NMR (CDCl₃): δ 7.83 (m, 2H); 7.77 (m, 2H); 7.65 (m, 1H); 7.50-7.45 (m, 4H); 3.85 (q, 1H, J=8Hz); 2.3 (s, 3H); 1.40 (d, 3H, J=8Hz).

Example 6

(R) (-)-dimethyl 3-(4-isobutylphenyl)-2-oxobutan-1-phosphonate

15 A solution of (R) (-)-ibuprofen (3.45 g) in ethyl ether, cooled to 5°C, is treated, dropwise, with a 0.6 M solution of diazomethane in ethyl ether, up to a persistent yellow colour. The solvent is removed under vacuum; the residual oil is purified by flash chromatography to yield 3.3 g of methyl (R) (-) 2-(4'-isobutylphenyl)-propionate.

Alternatively, 2.6 g of carbonyldiimidazole are added under stirring to a solution of R(-)
20 ibuprofen (3.45 g) in 10 mL of THF. The mixture is stirred for 1 h, the solvent is evaporated under vacuum, and the residual oil is purified by flash chromatography to yield 4.05 g of (R) (-) 2-(4'-isobutylphenyl)-propionylimidazolid.

In an inert-gas atmosphere, a solution of butyl lithium (1.56 M; 13.3 mL, 0.027 mol) in hexane is added dropwise to a solution of dimethyl methylphosphonate (3.69 g; 0.03 mol)
25 in anhydrous THF (10 mL) cooled to -70°C. The mixture is stirred for 15 min before addition, dropwise, of a solution in anhydrous THF (10 mL) of methyl ester or of imidazolid, prepared as previously described.

Upon completion of the dripping step, the reaction mixture is kept, under stirring, for 1 h at -70°C and then for 1 h at room temperature. The mixture is then cooled to -10°C, and
30 1.8 mL of glacial acetic acid is added dropwise. The solvent is removed under vacuum, the residue is diluted with water, and the mixture is repeatedly extracted with dichloromethane

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In an inert-gas atmosphere, a solution of butyl lithium (1.56 M; 13.3 mL, 0.027 mol) in hexane is added dropwise to a solution of dimethyl methylphosphonate (3.69 g; 0.03 mol) in anhydrous THF (10 mL) cooled to -70°C . The mixture is stirred for 15 min before addition, dropwise, of a solution in anhydrous THF (10 mL) of methyl ester or of imidazolide, prepared as previously described.

Upon completion of the dripping step, the reaction mixture is kept, under stirring, for 1 h at -70°C and then for 1 h at room temperature. The mixture is then cooled to -10°C , and 1.8 mL of glacial acetic acid is added dropwise. The solvent is removed under vacuum, the residue is diluted with water, and the mixture is repeatedly extracted with dichloromethane (4x50 mL). The organic extracts are dried on sodium sulfate; after evaporation of the solvent, the residue is purified on silica gel, eluted with AcOEt to yield, as a colourless oil, 3.02 g of (R) (-)-dimethyl 3-(4-isobutyl-phenyl)-2-oxobutan-1-phosphonate.

$[\alpha]_D = -171^{\circ}$ ($c=1$; CH_3OH); $^1\text{H-NMR}$ (CDCl_3): δ 7.03 (s, 4H); 4.1-3.9 (dd, 2H, $J_1=15\text{Hz}$, $J_2=8\text{Hz}$); 3.8 (s, 3H); 3.70 (m, 1H); 3.65 (s, 3H); 2.55 (d, 2H, $J=8\text{Hz}$); 1.75 (m, 1H); 1.50 (d, 3H, $J=8\text{Hz}$); 0.85 (d, 6H, $J=7\text{Hz}$).

Example 7

(R) (-) 2-(4-isobutylphenyl)-7-*tert*-butoxycarbonylamino-heptan-3-one.

A solution of ethyl 5-*tert*-butoxycarbonylamino-2-ethoxycarbonyl-pentanoate (WO 94/10127) (1.59 g) in 3 mL of methanol is added to 8 mL of a 0.63 N solution of LiOH.H₂O in water/methanol (1:1); the mixture is stirred for 12 h at room temperature. The mixture is diluted with 10 mL of a saturated solution of monosodium phosphate, and the excess of methanol is removed under vacuum. The mixture is extracted with ethyl acetate (2x10 mL); from the organic extracts, combined and dried on sodium sulfate, by evaporation of the solvent 1.4 g (4.8 mmol) of 5-*tert*-butoxycarbonylamino-2-ethoxycarbonyl-pentanoic acid are obtained.

To a solution of the acid (2.4 mmol) in 8 mL of anhydrous THF 0.27 g (2.4 mmol) of commercially available magnesium ethylate is then added, and the suspension is stirred at room temperature up to complete dissolution of the reagents to form the magnesium complex.

Then a solution of 0.3 g of (R) (-) 2-(4'-isobutylphenyl)-propionylimidazolide is added, and the mixture is stirred for 4 h at room temperature. The mixture is acidified by addition of a few mL of 50% aqueous AcOH, and the solvent is evaporated under vacuum. The

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